Rec'd PCT/PTO 16 NOV 2001

Corrected Version

Form PTO-1390 (REV 10-95) U S DEPARTMENT OF COMMERCE AND TRADEMARK OFFICE		ATTORNEY'S DOCKET NUMBER CFV-013 01 (19935-1301)
TRANSMITTAL LETTER TO THE UNITED STATES DESIGNATED/ELECTED OFFICE (DO/EO/US) CONCERNING A FILING UNDER 35 U.S.C. 371		U S. APPLICATION NO. (If known, see 37 CFR 1.5) 10/009314
INTERNATIONAL APPLICATION NO. ~~PCT/GB/01856~~ PCT/GB00/01856 RO	INTERNATIONAL FILING DATE May 18, 2000	PRIORITY DATE CLAIMED May 19, 1999

TITLE OF INVENTION
Release of Poorly Soluble Agents

APPLICANT(S) FOR DO/EO/US
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Applicant herewith submits to the United States Designated/Elected Office (DO/EO/US) the following items and other information:

1. ☒ This is the FIRST submission of items concerning a filing under 35 U.S.C. 371.
2. ☐ This a SECOND or SUBSEQUENT submission of items concerning a filing under 35 U.S C. 371.
3. ☒ This express request to begin national examination procedures (35 U.S.C. 371(f)) at any time rather than delay examination until the expiration.
4. ☒ A proper Demand for International Preliminary Examination was made by the 19th month from the earliest claimed priority date.
5. ☒ A copy of the International Application as filed (35 U.S C. 371(c)(2))
   a. ☒ is transmitted herewith (required only if not transmitted by the International Bureau)
   b. ☒ has been transmitted by the International Bureau
   c. ☐ is not required, as the application was filed in the United States Receiving Office (RO/US)
6. ☐ A translation of the International Application into English (35 U.S.C. 371(c)(2)).
7. ☐ Amendments to the claims of the International Application under PCT Article 19 (35 U.S C. 371(c)(3)).
   a. ☐ are transmitted herewith (required only if not transmitted by the International Bureau).
   b. ☐ has been transmitted by the International Bureau
   c. ☐ have not been made; however, the time limit for making such amendments has NOT expired
   d. ☐ have not been made and will not be made.
8. ☐ A translation of the amendments to the claims under PCT Article 19 (35 U.S.C. 371(c)(3)).
9. ☒ An oath or declaration of the inventor(s) (35 U.S.C. 371(c)(4)) (unexecuted)
10. ☐ A translation of the annexes to the International Preliminary Examination Report under PCT Article 36 (35 U.S C. 371(c)(5).

Items 11. to 16. below concern document(s) or information included:

11. ☐ An information Disclosure Statement under 37 CFR 1.97 and 1.98
12. ☐ An assignment document for recording. A separate cover sheet in compliance with 37 CFR 3.28 and 3.31 is included.
13. ☐ A FIRST preliminary amendment.
    ☐ A SECOND or SUBSEQUENT preliminary amendment.
14. ☐ A substitute specification
15. ☐ A change of power of attorney and/or address letter.
16. ☒ Other items of information.
    - PCT Request
    - International Preliminary Examination Report

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I, Michael Phelan, do hereby certify that the foregoing documents are being deposited with the United States Postal Service as Express Mail, postage prepaid, "Post Office to Addressee", in an envelope addressed to the Commissioner for Patents, Box PCT, Washington, D.C 20231 on this date of November 16, 2001

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U.S. APPLICATION NO. (If known, see 37 CFR 1.5)	INTERNATIONAL APPLICATION NO. PCT/GB/01856	ATTORNEY DOCKET NUMBER CFV-013 01 (19935-1301)

17. ☐ The following fees are submitted:

CALCULATIONS PTO USE ONLY

BASIC NATIONAL FEE (37 CFR 1.492(A)(1)-(5):

Search Report has been prepared by the EPO or JPO **$890.00**

International preliminary examination fee paid to USPTO (37 CFR 1.482) ..... $

No international preliminary examination fee paid to USPTO (37 CFR 1.482 but international search fee paid to USPTO (37 CFR 1.445(a)(2)) ..... $

Neither international preliminary examination fee (37 CFR 1 482) nor international search fee (37 CFR 1.445(a)(2)) paid to USPTO **$1040.00**

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NOTE: Where an appropriate time limit under 37 CFR 1.494 or 1.495 has not been met, a petition to revive (37 CFR 1.137(a) or (b)) must be filed and granted to restore the application to pending status.

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10/009314
PCT/GB00/01856

WO 00/71095

RELEASE OF POORLY SOLUBLE AGENTS

The present invention relates to a controlled release pellet composition for delivering a poorly soluble pharmaceutically active agent in a controlled manner over an extended period of time, typically over a period of 24 hours. The formulation is intended to enhance and control the release rate of agents, such as nifedipine, which are otherwise only poorly soluble in aqueous liquids.

Enhancement of the rate of dissolution of nifedipine has been the subject of research. Shu-Yang Yen et al (Drug Development and Industrial Pharmacy, 23(3), 313-317 (1997)) report that dissolution enhancement of nifedipine may be achieved by using super-disintegrants such as sodium starch glycolate, crospovidone and croscarmellose sodium. Nifedipine was formed into uncoated granules and tablets. Substantial dissolution was achieved within about 60 minutes. However, there is no report on the controlled release properties of these formulations.

Chowdray KPR and G. Girija Sankar (Drug Development and Industrial Pharmacy 23(3), 325-330 (1997)) describe the microencapsulation of nifedipine with Eudragit RL PM (a water-insoluble acrylic polymer). The core contained in addition to nifedipine, hydroxypropylmethyl cellulose and microcrystalline cellulose. Release of nifedipine over a period of 12 hours was reported.

The bioavailability of cores containing nifedipine and hydroxypropylmethyl cellulose phthalate together with

methacrylic acid-methacrylic acid methyl ester copolymer (Eudragit L) was investigated in animal studies reported in A. Hasegawa et al (Chem. Pharm. Bull.33(1) 388-391 (1985)).

US Patent 5,051,263 (Barry et al) describes a sustained release granule formulation comprising a core containing a poorly soluble active agent such as nifedipine, the core being coated with a mixture comprising a water insoluble but water swellable acrylic polymer and a water-soluble hydroxylated cellulose derivative. The core comprises the active agent, a carbomer (generic name for carboxypolymethylene) and microcrystalline cellulose.

It is an object of the present invention to provide improved controlled release formulations for use with pharmaceutical agents which are poorly soluble in water.

The present invention is based on the surprising discovery that the incorporation of a polyethylene glycol into the core improves the controlled release properties.

Thus, the present invention provides a controlled release pellet, which comprises:

- a core containing a poorly soluble pharmaceutically active agent and a polyethylene glycol;
- a coating around the core and comprising a water-soluble cellulose and a water-insoluble acrylic polymer.

The invention also relates to a corresponding method of forming the controlled release pellet.

The core may be formed in conventional manner as set out in, for example, patent specifications US 4,900,558, US

5,051,363 and US 5,055,306.

The core may also contain a disintegrant such as sodium starch glycolate, crospovidone and croscarmellose sodium. The amount of disintegrant is generally in the region 0-10% by weight, particularly 1-5% by weight.

In addition to the pharmaceutically active agent and the polyethylene glycol, the core generally also comprises a carrier such as a water-insoluble swellable cellulose, such as microcrystalline cellulose. A pH modifier, such as sodium bicarbonate, dibasic calcium phosphate, citric acid or tris(hydroxymethyl)aminomethane (Tris), may be included in the core to buffer the core to a pH which gives preferred dissolution characteristics for the active agent. This may be used to improve the solubility of certain poorly soluble active agents. Where the pellets are to be formed into tablets, a proportion of a water insoluble or pH sensitive acrylic polymer may also be included in the core to maintain the preferred dissolution rate after compression. The amount of carrier in the core is preferably in the region 0-70% by weight, particularly 10-60% by weight. The amount of water insoluble acrylic polymer in the core is preferably in the region 0-50% by weight, particularly 10-30% by weight.

Generally, the cores have a size in the range 0.5 to 2.0mm, preferably 0.5 to 1.4mm.

The polyethylene glycol which is included in the core has been found to enhance the dissolution rate of the poorly soluble active agent and also to assist in providing

controlled release. Polyethylene glycols are well known in the art and include a repeating $-(CH_2CH_2O)-$ group with various terminal groups. Polyethylene glycols are categorised according to their nominal molecular weight and in the present invention nominal molecular weights of 1000 to 8000 (i.e. PEG 1000 to PEG 8000) are preferred. The polyethylene glycol is generally a solid at room temperature but is melted prior to formulation. Usually, the amount of polyethylene glycol in the core is in the range 5-50% by weight, particularly 10-30% by weight.

The amount of polyethylene glycol required is to an extent dependent on the amount of active agent present and it is preferred that the ratio of polyethylene glycol to active agent lies in the range 0.5 to 2.0:1 by weight.

The poorly soluble pharmaceutically active agent is typically nifedipine or other poorly soluble active agent such as glibenclamide, griseofulvin oxaprozin, ibuprofen, diclofenac, or nabumetone. The active agent is generally present in an amount of 1-90% by weight, typically 5-70% by weight of the core weight. The solubility of the poorly soluble active agent in water is generally less than 1mg/ml at room temperature and pH7. The solubility of nifedipine is less than 0.1mg/ml.

The coating around the core controls release of the active agent from the core itself (in conjunction with the properties of the core matrix). The coating comprises a mixture of a water soluble cellulose and a water insoluble acrylic polymer. The ratio of water insoluble agent to

water soluble agent is a factor controlling the release rate and the ratio is generally in the range of 1:1 to 10:1, generally 5:3 to 5:1 respectively. The water insoluble acrylic polymer is preferably neutral and may comprise a homopolymer or copolymer, for instance of acrylic acid esters or methacrylic acid esters. Usually, the acrylic polymer is provided as an aqueous dispersion. A particularly suitable acrylic polymer is sold under the trademark Eudragit NE30D and comprises a copolymer of acrylic and methacrylic acid esters and is usually supplied as an aqueous dispersion containing approximately 30% by weight solids.

The water soluble cellulose may be a hydroxylated cellulose derivative, such as hydroxypropylmethyl cellulose, typically having a degree of substitution of 28-30% of methoxy groups and 7-12% of hydroxypropyl groups. Hydroxypropyl, hydroxyethyl or hydroxymethyl celluloses may also be used.

The coating preferably comprises from 3-40% by weight, preferably 5-25% by weight of the pellet.

Since active agents such as nifedipine may interact with food in the stomach, in a particularly preferred embodiment the pellet is further coated with an enteric coating. Enteric coatings are well known in the art and typically comprise an acid-resistant agent.

If necessary, the pellets of the present invention may be formed into tablets together with conventional tableting agents.

Embodiments of the present invention will now be described by way of example only.

Example 1

Cores containing nifedipine and polyethylene glycol (PEG4000) having the formulations set out in Table 1 were prepared as described below.

Table 1 (Core Formulation)

Material	Quantity (g)
Nifedipine USP (surface area of approx.0.8m^2/g)	225.3
Polyethylene Glycol 4000 USPNF	225.0
Microcrystalline Cellulose USPNF (Avicel PH101)	530.2
Croscarmellose Sodium USPNF (Ac-Di-Sol)	20.1
Purified Water	405.1

The cores were coated with two coating suspensions. The first coating suspension functioned as a release rate controlling coat and had the formulation as set out in Table 2. The coating suspension contained 20%w/w solid material and the weight of suspension added was equivalent to 5% of the core weight.

Table 2- First Coating Suspension (Release Rate Controlling Coat)

Material	Quantity (g)
Poly(ethylacrylate, Methylmethacrylate) 2:1 (Eudragit NE30D)	293.8
Hydroxypropylmethylcellulose (Pharmacoat 603)	53.1
Talc	58.9
Purified Water	596.9

A second (enteric) coating was also applied. The second coating suspension is shown in Table 3 and contained 20%w/w solid material. The weight of suspension added was equivalent to 10% of the core weight.

Table 3 - Second Coating Suspension (Enteric Coat)

Material	Quantity (g)
Poly(methacrylic acid, ethylacrylate) 1:1 (Eudragit L30D-55)	416.8
Talc	62.6
Triethyl Citrate	12.5
Purified Water	508.7

(a) Core Production

A 1kg batch of cores (batch 5507:00198) was produced as follows. Molten PEG4000 was weighed into a pre-heated mixing bowl of a Erweka AR401 planetary mixer at a temperature of 90°C. Nifedipine was added over a period of 1 to 2 minutes at a mixing speed of approximately 180rpm and the mixture mixed for a further 2 to 3 minutes. Ac-Di-

Sol was dispersed in the batch quantity of water and added to the nifedipine/PEG4000 mixture over 4 minutes at 100rpm. Avicel PH101 was added and mixed over a period of 7 to 8 minutes at 100rpm to produce a wet mass. The wet mass was covered and allowed to cool for approximately 30 mins to 29°C. Then the wet mass was extruded through a 0.8mm screen of a Niro Fielder E140 extruder at a feeder speed of approximately 45rpm and an impeller speed of approximately 30rpm. The extrudate was collected and spheronised for 12.5 minutes in a Niro Fielder S450 spheroniser at approximately 400rpm. The spheres were collected and dried at approximately 55°C in an Aeromatic Fielder Strea 1 fluid bed drier. The dried cores were sieved to between 0.5 and 1.4mm to remove fines and large agglomerates.

(b) Coated Pellet Production

A batch size of 600g of the cores was coated to produce pellets (batch 5509:00198) as follows. The first coating suspension was prepared by dissolving hydroxypropylmethyl cellulose (Pharmacoat 603) in approximately 450g of purified water and mixing with a low shear mixer for approximately 2 hours. Talc was added and dispersed using a Silverson SL2 hi-shear mixer for approximately 30 mins. This mixture was added to the Eudragit NE30D, made up to 1000g with the remaining purified water and stirred for 20 minutes at approximately 350rpm using a Heidolph RZR2051 mixer until uniform.

The second coating suspension was prepared by

dispersing the triethyl citrate and talc in approximately 300g of purified water using a Silverson SL2 hi-shear mixer for 7 minutes, adding to Eudragit L30D-55 and the remaining water and stirring at approximately 350rpm for 6 minutes using a Heidolph RZR2051 mixer until uniform.

The first coating suspension was added to the batch of cores in an Aeromatic Fielder Strea 1 fluid bed drier using a 0.8mm spray gun nozzle at 8g/min (1 bar atomising pressure, inlet temperature 35°C and airflow of 90m^3/hr) to form a first coat. The second coating suspension was added immediately thereafter using a 1.1mm spray gun nozzle at approximately 11g/min (1 bar atomising pressure, inlet temperature 35°C and airflow of approximately 100m^3/hr) to form a second coat. The coated cores were placed in an LTE Vulcan 150 oven to cure at approximately 45°C for approximately 20 hours. The coated cores were sieved through a 1.4mm screen to remove agglomerates. The pellets so produced were then stored.

(c) Release Profiles

Figure 1 shows the release profile of the coated core of the invention in 900ml of a dissolution medium containing 1% sodium lauryl sulphate and 1% propanediol in simulated gastric fluid (37°C and 100rpm. stirring). It will be noted that there is good controlled release over the 24 hour period shown.

Example 2 (Comparison)

For comparison purposes, four batches of uncoated nifedipine-containing cores were prepared as in Example 1 having the composition set out in Table 4.

Table 4 (uncoated cores)

Material / Batch	Content (g)			
	DNIF97/004	DNIF97/041	DNIF97/043	DNIF98/023
Nifedipine	240.6	225.7	200.9	490.3
Molten PEG 4000	0	225.5	250.3	0
Ac-Di-Sol	0	20.2	0	19.9
Avicel PH101	959.8	529.9	550.7	490.3
Water	1080.0	341.4	321.0	793.8

The formulation DNIF97/041 is substantially the same as the uncoated core of Example 1.

Figure 2 shows the release profiles in vitro (determined as in Example 1). It can be seen that the presence of both the polyethylene glycol and the croscarmellose sodium (Ac-Di-Sol) enhance the release rate of nifedipine. Both of these additives are preferred to provide a sufficiently fast dissolution rate of the uncoated pellet cores such that control can be exercised over the final release rate by addition of a rate controlling coating.

Example 3

Uncoated Oxaprozin containing cores were manufactured as detailed in Example 1. The composition of these uncoated cores is summarised in Table 5.

Table 5: Core Formulation of Oxaprozin Pellets				
Materials & Batch Nos.	Content(g)			
	DPZ00/001	DPZ00/003	DPZ00/004	DPZ00/005
Oxaprozin	225.0	226.1	225.1	225.8
Molten PEG 4000	224.5	225.9	0	0
Ac-Di-Sol	20.1	0	20.0	0
Avicel PH101	529.9	549.6	755.5	775.2
Water	483.8	407.8	949.6	873.4

Pellets were sieved to between 0.5 and 1.4mm and further processed by coating with a suspension in order to produce a release rate controlling membrane. The composition of the coating suspension applied is detailed in Table 6. The coating suspension contained 20% w/w solid material and the weight of suspension applied was equivalent to 25% of the initial core weight.

Table 6: Core Formulation of Oxaprozin Pellets	
Materials	Quantity(g)
Eudragit NE30D	784.8
Hydroxypropylmethylcellulose	7.8
Talc	156.7
Water	To 2003.5

Oxaprozin release was studied in-vitro in 0.05M KH_2PO_4 buffer (pH 8.0, 37°C, 100rpm). Samples were taken manually and Oxaprozin determined by HPLC (Acetonitrile: H_2O 45:55 with 2.5ml/L Acetic acid; Nucleosil ODS 10μm 250 x 4.6mm, flow rate - 1.5ml/min; 250nm). The resulting release profiles are summarised on Figure 3. It will be noted that the effect of polyethylene glycol and Ac-di-sol follows broadly the same trend as seen in Example 2. That is to say that the rate of release is increased in the presence of Ac-di-sol and further by the presence of PEG and Ac-di-sol. However, PEG alone has only a small effect in this case.

Example 4

Uncoated Ibuprofen containing cores were manufactured as detailed in Example 1. The composition of these uncoated cores is detailed in Table 7.

Table 7: Core Formulation of Ibuprofen Pellets

Materials & Batch Nos.	Content(g)			
	DIB99/023	DIP99/025	DIB99/026	DIB99/029
Ibuprofen	224.8	225.3	225.2	225.7
Molten PEG 4000	226.5	225.1	0	0
Ac-Di-Sol	20.2	0	20.2	0
Avicel PH101	530.5	550.0	755.4	777.0
Water	491.7	423.4	1002.8	903.8

Pellets were sieved to between 0.5mm-1.4mm and further processed by coating with a suspension to produce a release rate controlling membrane. The composition of this suspension is detailed in Table 8. The coating suspension contained 20% w/w solid material and the weight of suspension applied was equivalent to 12% of the initial core weight.

Table 8: Coating Solution used for Ibuprofen Pellets

Materials	Quantity(g)		
	DIB99/023c1 & 025c1	DIP99/026c1	DIB99/029c1
Eudragit NE30D	784.6	785.2	392.3
Hydroxypropylmethyl cellulose	7.8	7.9	4.1
Talc	156.8	156.6	78.4
Water	to 1999.3	To 2000.7	To 1005.3

Ibuprofen release was studied in-vitro in 0.05M KH_2PO4 (pH 6.8, 0.05M, 30°C, 100rpm). Ibuprofen was determined spectrophotometrically (264nm). The resulting release profiles are summarised in Figure 4. It will be noted that the effect of polyethylene glycol and Ac-di-sol follows the same trend as seen in Example 2. That is to say that the rate of release is increased in the presence of PEG, is increased still further by Ac-di-sol and is greatest in the presence of both PEG and Ac-di-sol.

Example 5

Uncoated Diclofenac sodium containing cores were manufactured as detailed in Example 1. The composition of these cores is detailed in Table 9.

Table 9: Core Formulation of Diclofenac Sodium Pellets				
Materials & Batch Nos.	Content(g)			
	DDF00/003	DDF00/004	DDF00/005	DDF00/006
Diclofenac Sodium	165.7	165.8	165.3	165.3
Molten PEG 4000	0	0	165.6	165.2
Ac-Di-Sol	20.1	0	20.1	0
Avicel PH101	816.0	836.1	650.2	670.5
Water	1013.2	932.3	412.2	401.6

Pellets were sieved to between 0.5mm-1.4mm and further processed by coating with a suspension to form a release rate controlling membrane. The composition of this suspension is detailed in Table 10. The coating suspension contained 20% w/w solid material and the weight of suspension added was equivalent to 25% of core weight.

Table 10: Coating Solution used for Diclofenac Sodium Pellets	
Materials	Quantity(g)
Eudragit NE30D	790.5
Hydroxypropylmethyl Cellulose	4.7
Talc	158.2
Water	To 1999.5

Diclofenac release was studied in-vitro in 0.05M KH_2PO_4 buffer (pH 6.8, 37°C and 100rpm). Samples were taken

Diclofenac release was studied in-vitro in 0.05M KH_2PO_4 buffer (pH 6.8, 37°C and 100rpm). Samples were taken manually and Diclofenac determined spectrophotometrically (248nm). The resulting release profiles are summarised in Figure 5. It will be noted that the effect of polyethylene glycol and Ac-di-sol follows the same trend as seen in Example 2. That is to say that the rate of release is increased in the presence of PEG, is increased still further by Ac-di-sol and is greatest in the presence of both PEG and Ac-di-sol.

Example 6 (Various PEG's)

Uncoated Diclofenac Sodium containing cores were manufactured as detailed in Example 1. These cores contained PEG 6000 which replaced the PEG 4000 used in Example 5. The formulation of the uncoated cores is detailed in Table 11.

Table 11: Core Formulation of Diclofenac Sodium Pellets

Materials & Batch Nos.	Content(g)	
	DDF00/001	DDF00/002
Diclofenac Sodium	165.5	165.5
Molten PEG 6000	165.2	165.8
Ac-Di-Sol	20.1	0
Avicel PH101	650.5	670.3
Water	405.9	401.0

Pellets were sieved to between 0.5mm - 1.4mm and coated with a suspension to form a release rate controlling membrane. The composition of this suspension is summarised in Table 12. The suspension contained 20% solid material and the weight of suspension added was equivalent to 25% of core weight.

Table 12: Coating Solution used for Diclofenac Sodium Pellets	
Materials	**Quantity(g)**
Eudragit NE30D	395.1
Hydroxypropylmethyl cellulose	2.5
Talc	79.1
Water	1013.2

Diclofenac release was studied in-vitro in 0.05M KH_2PO_4 buffer (pH 6.8, 37°C and 100rpm). Samples were taken manually and Diclofenac determined spectrophotometrically (248nm). The resulting release profiles are summarised in Figure 6. The effect of PEG 6000 is similar to that of PEG 4000. This can be seen from the superimposition of the profiles obtained from pellets containing these two components. Furthermore the effect of PEG 4000 and 6000 is potentiated in the presence of Ac-di-sol in line with other examples.

Example 7

Uncoated Glibenclamide containing cores were manufactured as detailed in Example 1. The formulation of the uncoated cores is detailed in Table 11.

Table 13 Core Formulation of Glibenclamide Pellets				
Materials	Content(g)			
	DGLB99/001	DGLB99/002	DGLB99/003	DGLB99/004
Glibenclamide	225.1	225.7	225.2	225.6
Molten PEG 4000	226.0	225.3	0	0
Ac-Di-Sol	19.9	0	20.0	0
Avicel PH101	530.1	550.5	755.2	774.9
Water	464.9	413.3	927.0	797.6

Pellets were sieved to between 0.5mm-1.4mm and further processed by coating with a suspension to form a release rate controlling membrane. The composition of this suspension is detailed in Table 14. The coating suspension contained 20% w/w solid material and the weight of suspension applied was equivalent to 25% of core weight.

Table 14: Coating Solution used for Glibenclamide Pellets	
Materials	Quantity(g)
Eudragit NE30D	791.4
Hydroxypropylmethyl cellulose	4.7
Talc	158.3
Water	To 2001.9

Glibenclamide release was studied in 0.01M NaOH (37°C,100rpm). Glibenclamide was determined spectrophotometrically (229nm). The resulting release profiles are summarised in Figure 7. It will be noted that the effect of polyethylene glycol and Ac-di-sol follows the same trend as seen in Example 2. That is to say that the rate of release is increased in the presence of PEG, is increased still further by Ac-di-sol and is greatest in the presence of both PEG and Ac-di-sol.

The following are trademarks: Avicel, Ac-Di-Sol, Eudragit and Pharmacoat.

CLAIMS

1. A controlled release pellet, which comprises:

- a core containing a poorly soluble pharmaceutically active agent and a polyethylene glycol;
- a coating around the core and comprising a water soluble cellulose and a water insoluble acrylic polymer.

2. A pellet according to claim 1, wherein the core further contains a disintegrant.

3. A pellet according to claim 2, wherein the disintegrant is croscarmellose sodium.

4. A pellet according to claim 2, wherein the disintegrant is sodium starch glycolate or crospovidone.

5. A pellet according to any of claims 2 and 4, wherein the disintegrant is present in an amount of 1 to 5% by weight of the core.

6. A pellet according to any preceding claim which further contains a carrier which is a water-insoluble swellable cellulose.

7. A pellet according to claim 6, wherein the carrier is present in an amount of 10 to 60% by weight of the core.

8. A pellet according to any preceding claim wherein the polyethylene glycol has a nominal molecular weight of 1000 to 8000.

9. A pellet according to claim 8 wherein the polyethylene glycol is present in an amount of 5 to 50% by weight of the core.

10. A pellet according to claim 9 wherein the polyethylene glycol is present in an amount of 10 to 30% by weight of the core.

11. A pellet according to any preceding claim wherein the ratio of polyethylene glycol to active agent is in the range 0.5 to 2.0:1 by weight.

12. A pellet according to any preceding claim wherein the active agent is nifedipine, glibenclamide, griseofulvin, oxaprozin, ibuprofen, diclofenac or nabumetone.

13. A pellet according to claim 12 wherein the active agent is present in an amount of 5 to 70% by weight of the core.

14. A pellet according to any preceding claim wherein the active agent has a solubility in water of less than 1mg/ml at room temperature and pH7.

15. A pellet according to any preceding claim wherein the ratio of water insoluble acrylic polymer to water soluble cellulose in the coating is in the range 1:1 to 10:1 respectively.

16. A pellet according to any preceding claim wherein the coating comprises 3 to 40% by weight of the pellet.

(12) INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(19) World Intellectual Property Organization
International Bureau

(43) International Publication Date
30 November 2000 (30.11.2000)

PCT

(10) International Publication Number
WO 00/71095 A2

(51) International Patent Classification[7]: A61K 9/00

(21) International Application Number: PCT/GB00/01856

(22) International Filing Date: 18 May 2000 (18.05.2000)

(25) Filing Language: English

(26) Publication Language: English

(30) Priority Data:
9911546.1 19 May 1999 (19.05.1999) GB

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(81) Designated States *(national)*: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CR, CU, CZ, DE, DK, DM, DZ, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZW.

(84) Designated States *(regional)*: ARIPO patent (GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG).

Published:
— *Without international search report and to be republished upon receipt of that report.*

For two-letter codes and other abbreviations, refer to the "Guidance Notes on Codes and Abbreviations" appearing at the beginning of each regular issue of the PCT Gazette.

WO 00/71095 A2

(54) Title: RELEASE OF POORLY SOLUBLE AGENTS

(57) Abstract: A controlled release pellet for releasing a poorly soluble active agent comprises a core containing the active agent (e.g. nifedipine, glibenclamide, griseofulvin, oxaprozin, ibuprofen, diclofenac, nabumetone etc.), a polyethylene glycol and a carrier; the core having a coating comprising a water soluble cellulose and a water insoluble acrylic polymer. A disintegrating agent is preferably included in the core.

Figure 1

Release of Coated Nifedipine OSAT Pellet Batch 5509 : 00198

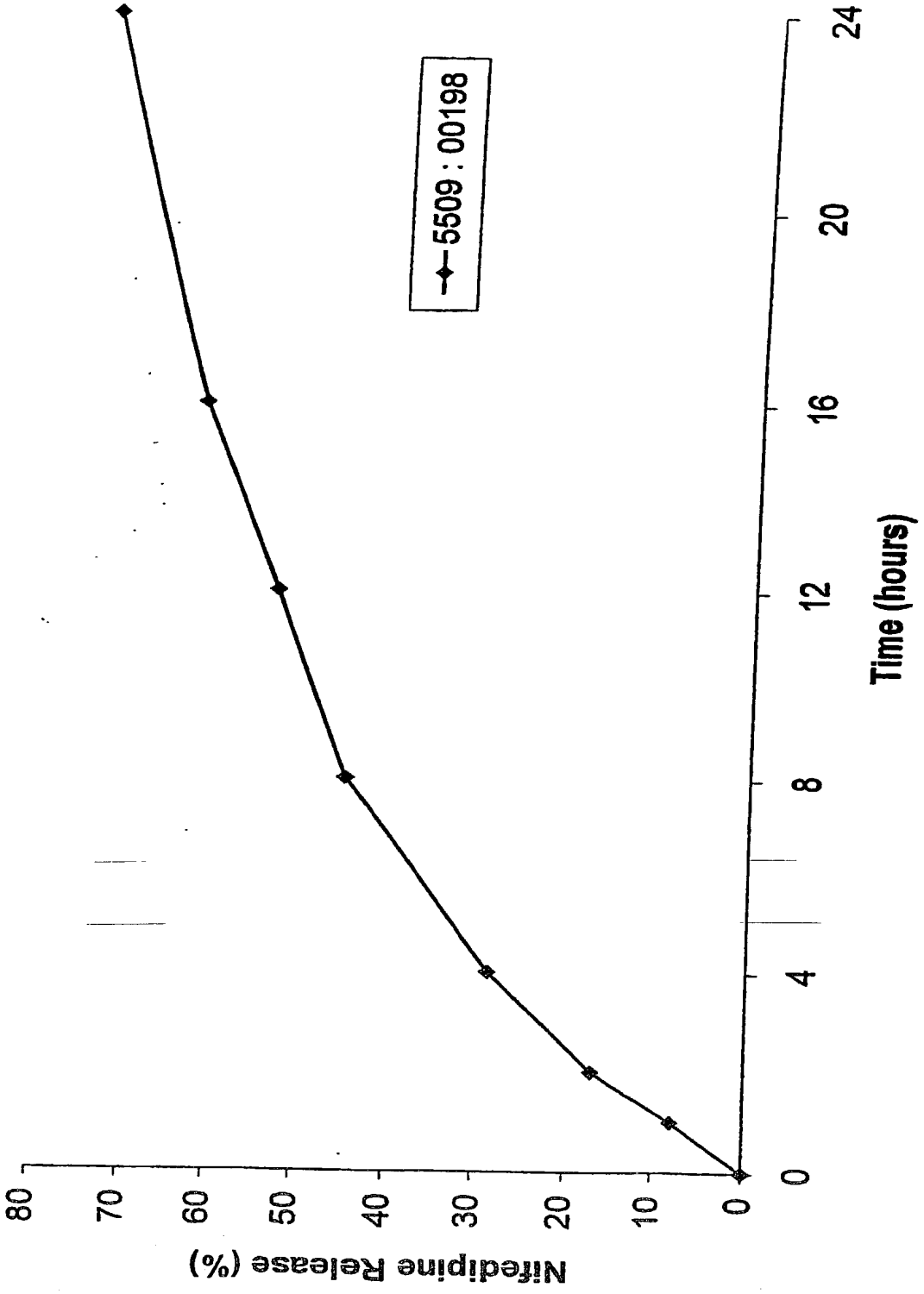


Figure 2
Release Profile of 4 Uncoated Nifedipine OSAT Pellet Batches With or Without PEG4000 and/or Ac-Di-Sol

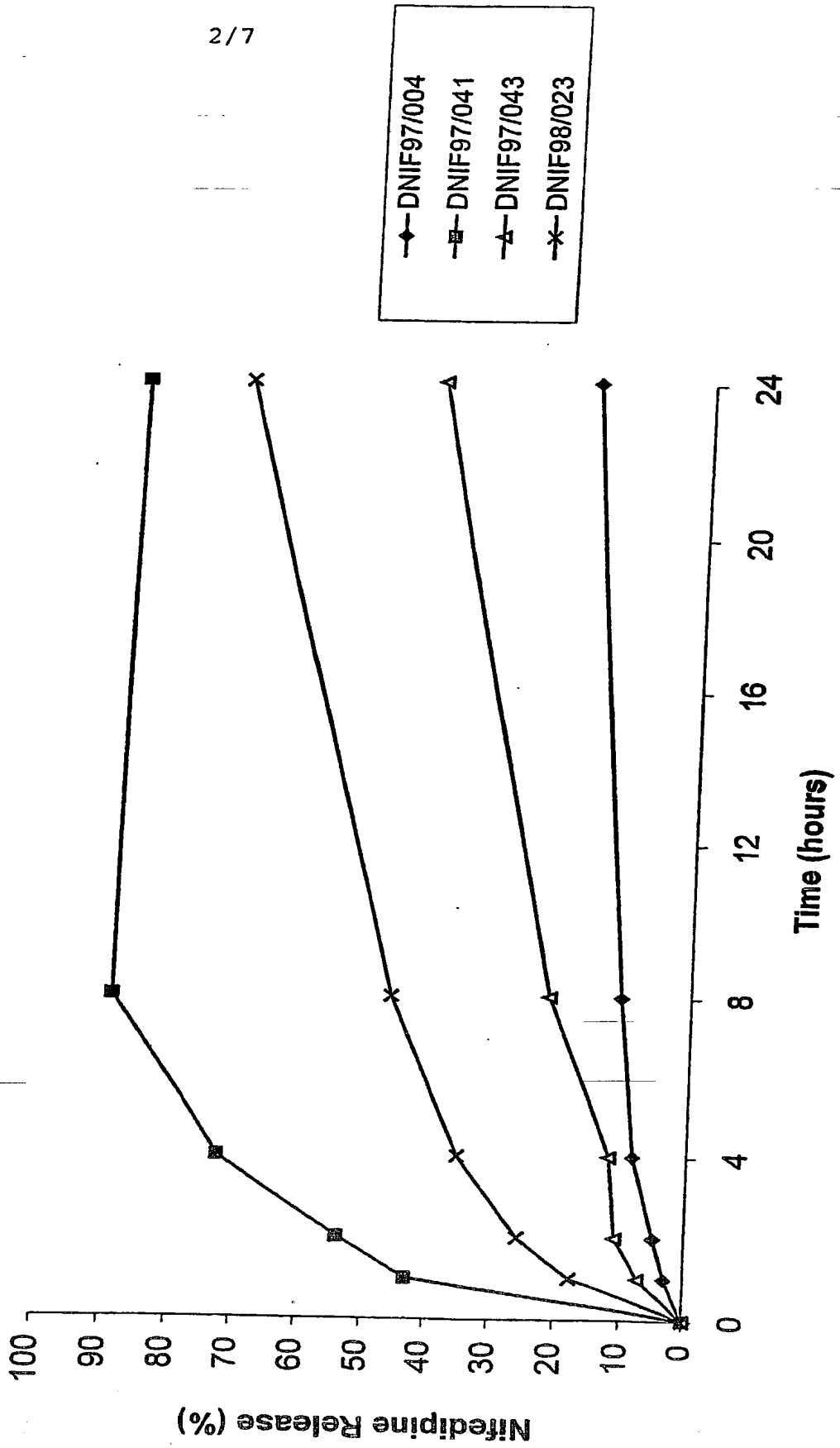


Figure 3
Oxaprozin release in the presence of PEG 4000 and Ac-di-sol

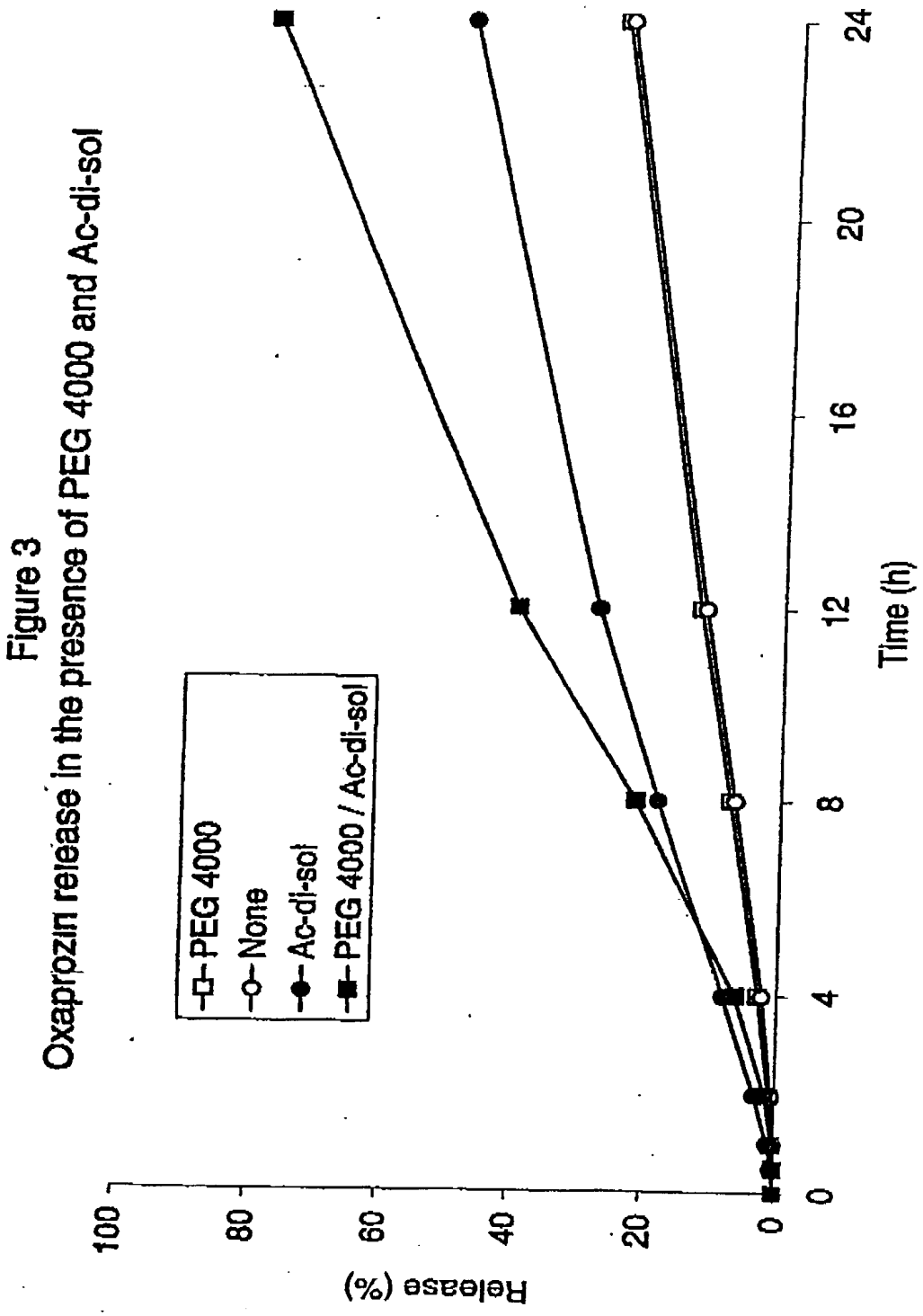
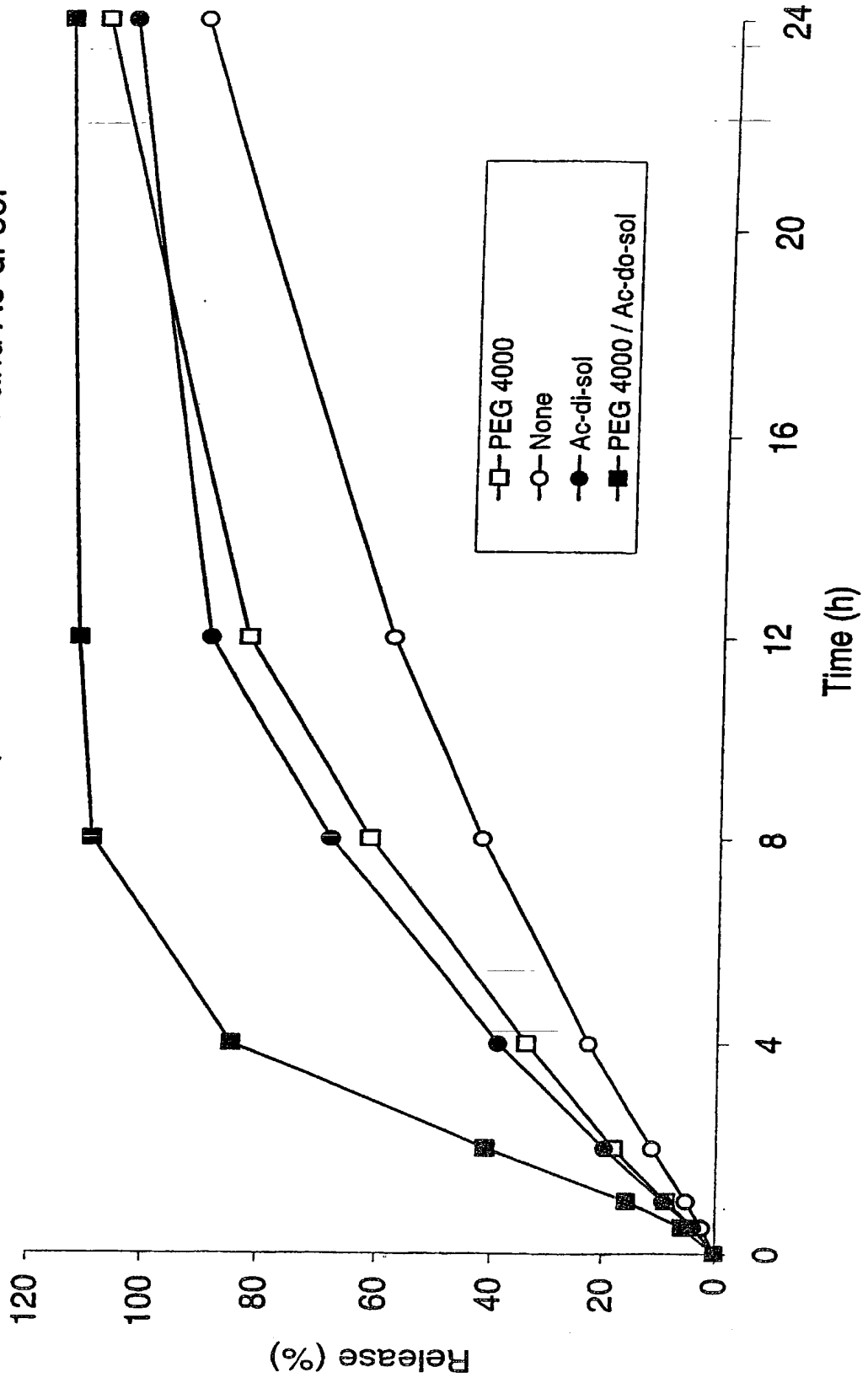


Figure 4
Ibuprofen release in the presence of PEG 4000 and Ac-di-sol



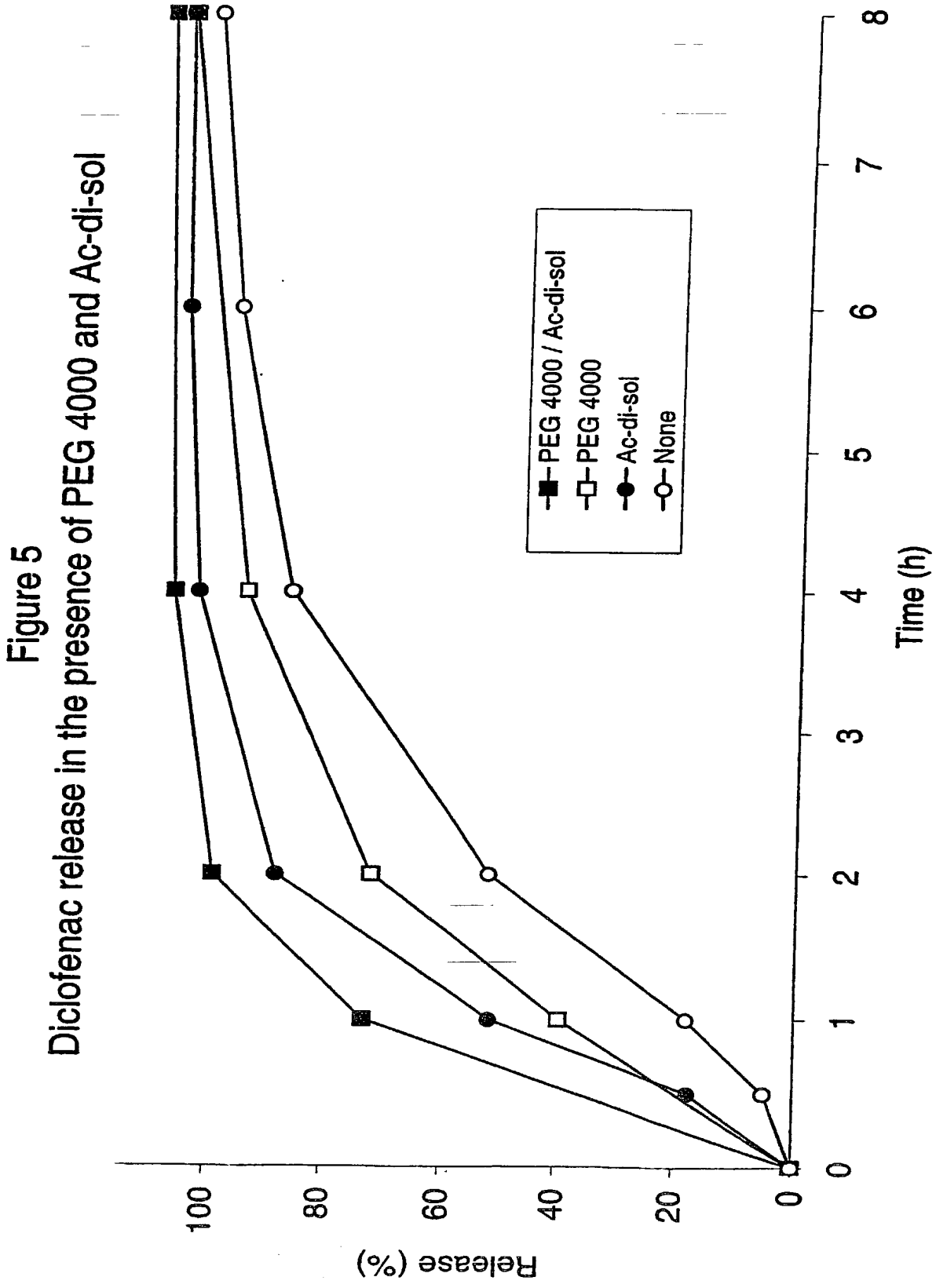
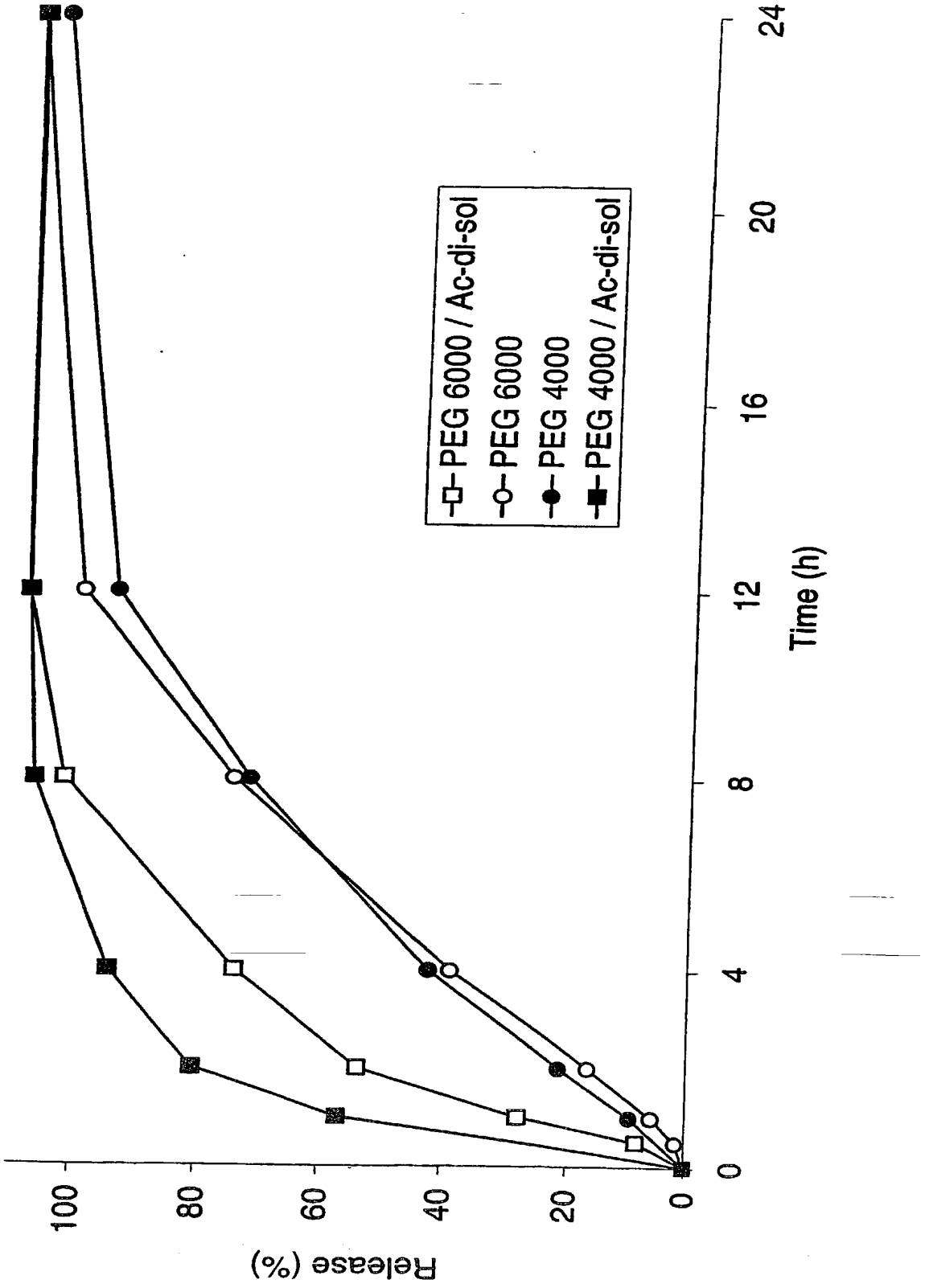


Figure 5
Diclofenac release in the presence of PEG 4000 and Ac-di-sol

Figure 6
Diclofenac release in the presence of PEG 6000/4000 and Ac-di-sol



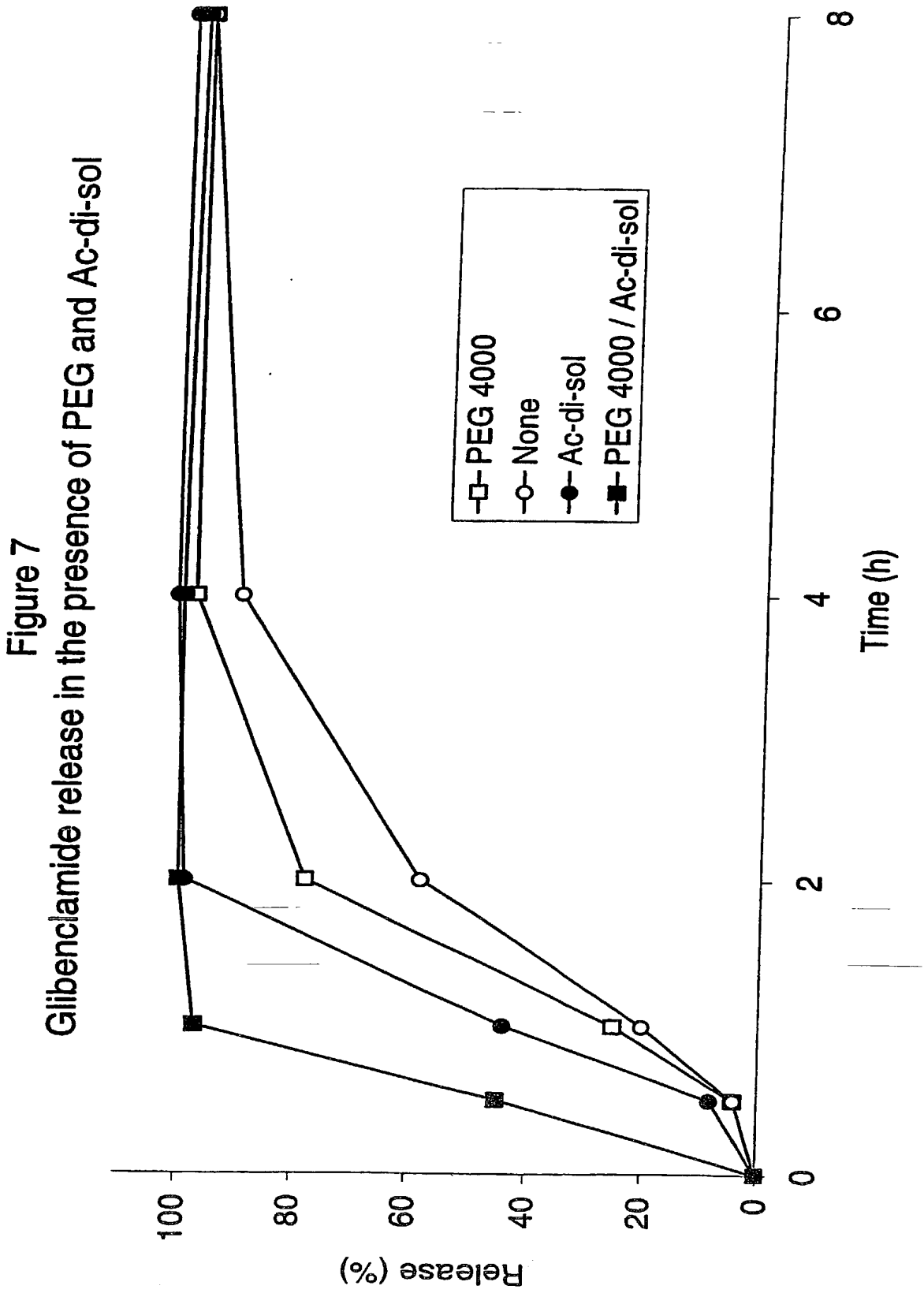


Figure 7
Glibenclamide release in the presence of PEG and Ac-di-sol

DECLARATION FOR PATENT APPLICATION

As a below-named inventor, I hereby declare that:

My residence, post office address, and citizenship are as stated below next to my name.

I believe I am the original, first and sole inventor (if only one name is listed below) or an original, first and sole inventor (if more than one name is listed below) of the subject matter which is claimed and for which a patent is sought on the invention entitled:

RELEASE OF POORLY SOLUBLE AGENTS

the specification of which (check one): ☐ is attached hereto PCT/GB00/01856
☒ was filed on 18 May 2000 as Serial No. _____, and
was amended on _____ (if applicable).

I hereby state that I have reviewed and understand the contents of the above-identified specification, including the claims, as amended by any amendment referred to above.

I acknowledge the duty to disclose information which is material to the examination of this application in accordance with 37 CFR § 1.56(a).

Prior Foreign Application(s): I hereby claim foreign priority benefits under 35 USC § 119 of any foreign application(s) for patent or inventor's certificate listed below, and have also identified below any foreign application for patent or inventor's certificate having a filing date before that of the application on which priority is claimed:

Application No.	Country	Day/Month/Year Filed	Priority Claimed
9911546.1	UK	19/5/1999	[X] Yes [ ] No
			[ ] Yes [ ] No
			[ ] Yes [ ] No

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I hereby claim the benefit under 35 USC §120 of any United States application(s) or any PCT international application(s) designating the United States of America listed below and, insofar as the subject matter of each of the claims of this application is not disclosed in the prior United States or PCT international application in the manner provided by 35 USC §112, first paragraph, I acknowledge the duty to disclose material information as defined in 37 CFR §1.56(a) which occurred between the filing date of the prior application and the national or PCT international filing date of this application:

U.S. Application Serial No.	U.S. Filing Date	Status (patented, pending, abandoned)

I hereby declare that all statements made herein of my own knowledge are true and that all statements made on information and belief are believed to be true; and further, that these statements are made with the knowledge that wilful false statements and the like so made are punishable by fine or imprisonment, or both, under 18 USC §1001, and that such willful false statements may jeopardize the validity of the application or any patent issued thereon.

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